REMARKS

I. Amendments to the Claims

Claim 7 has been amended to recite a method for treating insufficiency of peripheral circulation or peripheral angiostenosis *in a peripheral muscle* of a subject for which HGF is effective, comprising administering intramuscularly *to the peripheral muscle* of the subject an expression vector containing a HGF gene. Pages 13 and 14 of the specification describe direct intramuscular administration of HGF to the target organ.

Claim 7 has also been amended to require that the expression vector contains a *constitutive promoter operably linked* to the HGF gene. HGF expression vectors containing constitutive promoters are described in the specification, such as in the Examples.

Claim 8 has been amended by deleting recitation of the viral expression vector, such that the claim now recites only the non-viral expression vector. New claim 11, directed to the viral expression vector, has been added.

Claim 9 has been amended by deleting the phrase "the membrane of which may be further fused to attenuated Sendai virus particles." New claim 10, reciting the limitation previously recited in claim 9, has been added.

No new matter has been added, and Applicants respectfully request entry of the amendments to the claims.

II. Objections to the Specification

A. Priority

At page 2 of the Office Action, the Examiner noted that the first paragraph of the specification should be amended to correct and update the priority information.

The specification has been amended herein as required by the Examiner.

Accordingly, Applicants respectfully request reconsideration and withdrawal of this objection.

B. Substitute Specification

At pages 2 and 3 of the Office Action, the Examiner stated that the Substitute Specification filed July 9, 2003 has not been entered, pending submission of a formal marked-up copy and proper explanation of the changes made in the Substitute Specification.

Applicants note that the Substitute Specification filed July 9, 2003 meets the rules that were in effect at that time. Specifically, the rules requiring submission of a red-lined copy of a Substitute Specification did not come into effect until July 30, 2003.

With regard to an explanation of the changes made in the Substitute Specification, Applicants submit that the changes are all editorial in nature and contain no new matter.

Thus, Applicants respectfully request reconsideration and withdrawal of this objection, and entry of the July 9, 2003 Substitute Specification.

III. Information Disclosure Statements

At page 3 of the Office Action, the Examiner stated that the references cited in Applicant's Information Disclosure Statements have all been considered.

However, the Examiner also indicated that many of the citations have been crossed-out, even though considered, because either: (i) the citation is improper in its content (e.g., missing author information), or (ii) because such citation is not a publicly available document, and therefore could not be listed on the front page of any patent that may issue.

Finally, the Examiner noted that if Applicants would like the publicly available references to be placed on the front page of a patent, Applicants should submit proper citations and/or the publicly available documents (with English translation, if needed).

Applicants note that the citations were in an acceptable form at the time the application was filed. However, so that the references will be placed on the front page of a patent, Applicants are submitting herewith a corrected PTO/SB/08 including proper citations for the published English language journal articles that have been crossed out.

III. Objections to the Drawings

At page 4 of the Office Action, the drawings were objected to for the following reasons:

A. Figs. 12-15

The Examiner indicated that for Figs. 12-15, the content of the two panels is not clearly explained in the brief description of the drawings (see page 6 of the specification).

In response, Applicants note that the top and bottom panels in Figs. 12-15 are 100- and 400-power micrographs, respectively. Therefore, the images shown in the top as compared to the bottom panel in each of Figs. 12-15 represent different levels of magnification, but the subject matter of the top and bottom panel is the same for each figure.

Thus, the brief description of the drawings clearly and accurately describes the content of both of the panels in each of Figs. 12-15.

B. Figs. 2 and 3

The Examiner also states that the meaning of the pound sign (i.e. "#") in Figs. 2 and 3 is not clear.

With regard to Fig. 2, Applicants note that the pound sign refers to the P value of less than 0.05 at the point of 100 ng/ml of HGF on the line graph, as described in Example 2 at page 24 of the specification. The asterisks also refer to P values that are defined in Example 2 of the specification. In order to clarify the meanings of the asterisks and the pound sign, Applicants have amended the Brief Description of the Drawings section of the specification to include the description of the asterisks and pound sign in Fig. 2.

With regard to Fig. 3, Applicants have amended the figure by deleting the asterisk and the pound sign from Fig. 3, and placing the language "P<0.01" and "P<0.05" into Figure 3.

These amendments are supported in the specification by Example 2 at page 25.

In view of the above, Applicants respectfully request reconsideration and withdrawal of the objections to the drawings.

IV. Statutory Double Patenting Objection

At page 4 of the Office Action, claim 8 was objected to under 37 C.F.R. § 1.75 as being a substantial duplicate of claim 7.

Specifically, the Examiner stated that all vectors are either viral or non-viral. The Examiner therefore concluded that claim 8, which limits the vector of claim 7 to either a viral vector or a non-viral vector, is substantially identical to claim 7.

In response, Applicants have amended claim 8 to recite only the non-viral expression vector, and added new claim 11 directed to a viral expression vector.

Thus, Applicants respectfully request reconsideration and withdrawal of the statutory double patenting objection.

V. Obviousness-Type Double Patenting Rejection

At page 5 of the Office Action, claims 7-9 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,248,722.

In response, Applicants are filing herewith a terminal disclaimer in this application, disclaiming any term that extends beyond the expiration date of the '722 patent, and promising to maintain common ownership of the instant application and the '722 patent.

Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

V. Claim Rejections Under 35 U.S.C. § 112, Second Paragraph - Indefiniteness

At pages 6 and 7 of the Office Action, claim 9 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Specifically, the Examiner contended that the limitation "the membrane of which may be further fused to attenuated Sendai virus particles" makes it unclear if such limitation is meant to limit the claim or not.

In response, Applicants have deleted the phrase "the membrane of which may be further fused to attenuated Sendai virus particles" from claim 9, and instead placed this limitation in a new dependent claim (claim 10).

Accordingly, Applicants respectfully request reconsideration and withdrawal of this rejection.

VI. Claim Rejections Under 35 U.S.C. § 112, First Paragraph - Enablement

At pages 7-13 of the Office Action, claims 7-9 were rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement.

According to the Examiner, the specification does enable a method for treating insufficiency of peripheral circulation or peripheral angiostenosis in a subject for which HGF is effective, comprising administering to a peripheral muscle of the subject a plasmid vector comprising an HGF gene comprising a coding sequence for HGF operably linked to a

constitutive promoter, wherein the plasmid is encapsulated in an HVJ-liposome, and wherein further cells of the peripheral muscle express the HGF protein, which protein then acts to increase angiogenesis in the muscle to which the vector has been administered.

However, the Examiner stated that the specification does not reasonably provide enablement for any vector, any promoter, any peripheral circulation or angiostenosis, or any treatment non-local to the muscle of administration. The Examiner further stated that the present claims are overly broad because they encompass treating any circulation problem in any tissue, by administration to any muscle of the body, by any vector and any HGF gene, which means any expressible sequence, and necessarily encompass non-constitutive promoters and promoters with low activity.

1. Vectors

Applicants respectfully traverse the Examiner's position regarding enablement of expression vectors, for at least the following reasons.

As noted in detail at pages 14-16 of the Declaration of Dr. Morishita, originally filed February 11, 2000 in grandparent application 09/029,497 (now Pat. No. 6,248,722) and submitted herewith, the present specification indicates that any expression vector would be expected to function in the present invention.

In particular, the Examples in the present specification show that gene therapy using the HVJ-liposome method is highly effective, and that HGF is an extremely potent cell growth stimulator. Accordingly, the specification states that any dosage forms of the HGF gene,

including viral expression vectors and naked DNA, would be effective for gene therapy. Further, the literature evidence cited and summarized in the Declaration confirms that HGF gene therapy using the adenoviral vector is effective, and also that the naked-DNA method is effective for gene therapy using the HGF gene. Thus, the present specification enables the use of any expression vector for HGF gene therapy.

2. Promoter

With regard to promoters, the Examiner has indicated that the specification enables gene therapy using HGF operably linked to a constitutive promoter (see above). In this regard, Applicants have amended claim 7 to recite that the HGF gene is operably linked to a constitutive promoter.

However, Applicants respectfully submit that although a constitutive promoter was used in the Examples of the present specification, any kind of promoter which can function to induce the expression of HGF gene in the site wherein the HGF gene has been administered can be used in the present invention, regardless of whether the promoter is constitutive or non-constitutive. This conclusion is supported by the disclosure of the present application, in view of common knowledge among those of ordinary skill in the relevant art at the filing date of the application. Furthermore, it is apparent that, once the HGF gene has been expressed to produce HGF protein, the HGF protein can exhibit pharmacological activities such as angiogenesis.

Therefore, because the claimed invention is enabled using any kind of promoter, without limitation to a constitutive promoter, Applicants submit that Examiner's position regarding promoters is incorrect.

Nevertheless, Applicants have amended the present claims to recite constitutive promoters, merely to further prosecution and for the purpose of obtaining patent protection for the subject matter recited in the present claims. Thus, the amendment does not indicate Applicants' admission of the Examiner's assertion that the claimed invention does not satisfy the enablement requirement.

3. Administration site

The Examiner has indicated that the specification enables local treatment of peripheral muscle at the site of administration. In this regard, Applicants have amended the claims to recite methods for treating insufficiency of peripheral circulation or peripheral angiostenosis in a peripheral muscle by intramuscular administration to the peripheral muscle.

However, as discussed at page 13 of the Declaration of Dr. Morishita, HGF gene therapy according to the present invention is also effective in tissues other than peripheral tissues and peripheral muscle. Similar to above, Applicants note that the claims have been amended merely to further prosecution and for the purpose of obtaining patent protection for the subject matter recited in the present claims. Therefore, the claim amendment described above does not indicate Applicants' admission of the Examiner's assertion that the claimed invention does not satisfy the enablement requirement.

Applicants respectfully request reconsideration and withdrawal of the enablement rejection.

VII. Conclusion

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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Date: February 8, 2006

AMENDMENTS TO THE DRAWINGS

The attached two (2) sheets of the drawings (Figure 3) include the following changes:

Figure 3 has been amended by deleting the asterisk and the pound sign, and placing the language "P<0.01" and "P<0.05" into the figure.

Attachments: Replacement Sheet for Figure 3.

Annotated Sheet for Figure 3.

Inventor's name: Ryuichi MORISHITA, et al.
Title: Medicament comprising HGF gene
Application No.: 10/615,262
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SUGHRUE Reference No.: Q75926
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ANNOTATED SHEET

FIG.3

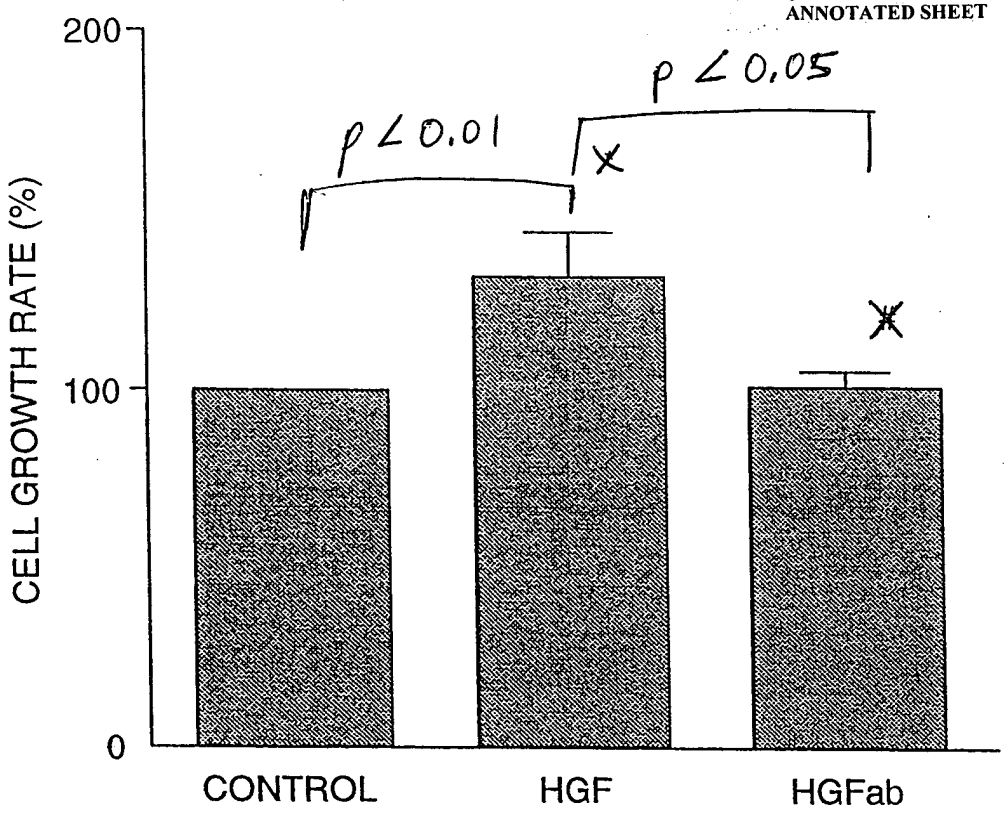

FIG.4